DETAILED ACTION

Priority

1. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

2. The drawings in this application have been accepted. No further action by Applicant is required.

Specification

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

4. The information disclosure statement filed on 1/23/2006 has been considered. An initialed copy is enclosed.

Election/Restrictions

5. Applicant's election with traverse of Group 1 claims 1-21 and 28-30 is acknowledged. The traversal is on the ground(s) that the composition containing c-di-GMP at page 5472, right column of Mayer et al., under "Materials and Methods" is merely a composition used in purifying cellulose synthase from bacterial cell and membrane components ruptured by a French press. Such a composition is not a pharmaceutical composition and could not be used as a pharmaceutical composition because it is neither sterile nor sufficiently purified from other contaminating bacterial components. Reconsideration and withdrawal of the restriction requirement is respectfully requested. This is found persuasive. Examiner withdraws the reference of Mayer et. Al. The technical feature of Group II is a pharmaceutical composition. The

technical feature of Group II is anticipated by Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129. Steinberger et al teach Jurkat cells were grown in the presence of 50μm if c-di-GMP in 96-well tissue culture plates thus Steinberger et al teach a pharmaceutical composition comprising c-di-GMP as an active ingredient and a pharmaceutically acceptable carrier (RPMI 1640 medium) (see Materials and Methods pg. 125). The special technical feature of Group I is a method of use of Group II, a pharmaceutical composition. Therefore Group II lacks unity with Group I because they do not have the same technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 22-25 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group II (claims 22-25), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement on 1/14/2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-16 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-16 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for attenuating the virulence of a microbial pathogen from S. aureus or for inhibiting or reducing colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, does not reasonably provide enablement for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims. The method claim is very broad and the product, a cyclic dinucleotide analogue thereof used to administer to a patient is directed to any microbial pathogen. Furthermore the claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Therefore it is hard for one skilled in the art to determine if a cyclic dinucleotide analogue can be used to attenuate the virulence, inhibit or reduce the colonization or any microbial pathogen in a patient. Since the specification fails to provide particular guidance for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any type of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Nature of the invention. The claims are drawn to for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on S. aureus biofilm formation (see 00101), the effects of c-di-GMP on S. aureus pre-formed biofilms (00102), c-di-GMP treatment the prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine S. aureus (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see 00116), the effect of c-di-GMP treatment on S. aureus pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that

indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120).

The state of the prior art. The state of the art is unpredictable with regard to administering cyclic dinucleotide analogue to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization in a patient. The state of the art questions the correlation between in vivo and in vitro models for treatment of bacterial/microbial pathogens. For example, Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach

that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al 2006 Journal of Bacteriology Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1 and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Additionally Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the

protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore the art questions whether any type of analogue would have the same effect on the method as claimed.

Furthermore the art has not shown any method of administering any type of a cyclic dinucleotide analogue thereof to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. The art questions the correlation between an in vivo and an in vitro model. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of the art is unpredictable in regards to administering any cyclic dinucleotide analogue thereof to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient.

Guidance in the specification. There is no showing in the specification that a cyclic dinucleotide analogue thereof can be administered to a patient to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen. Although the specification gives several examples of a method for inhibiting microbioal colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or a cyclic dinucleotide analogue there of on pre-formed microbial biofilm or biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3), the specification fails to show a method comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). Therefore the specification fails to describe any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof.

Working examples. The specification does not give any working example (i.e. challenged mice models or passive immunization approaches).

In conclusion, the claimed inventions are not enabled for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art has not shown any method of administering any cyclic dinucleotide analogue thereof to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. Furthermore, the art questions the correlation between an in vivo and an in vitro model. For the reasons set forth supra, the state of the art is unpredictable. There is also a lack of working examples. Although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

7. Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 17-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting S. aureus microbial colonization and S. areus biofilm formation or for reducing S. areus colonization and pre-formed S. areus microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to inhibit S. areus microbial colonization and S. areus biofilm formation or to reduce microbial colonization and pre-formed biofilm on said solid surface, does not reasonably provide enablement for any method for inhibiting any type microbial colonization and any type of biofilm formation or for reducing any type of colonization and pre-formed any type of microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a c-di-GMP or any cyclic dinucleotide analogue thereof to inhibit any type of microbial colonization and any biofilm formation or to reduce any microbial colonization and any pre-formed biofilm on said solid surface. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims. The method claim is very broad and the product, a c-di-GMP or a cyclic dinucleotide analogue thereof used in the method as set for supra to any type of microbial colonization or any type biofilm formation. Furthermore the claims are drawn to any method for inhibiting any type microbial colonization and any type of biofilm formation or for reducing any type of colonization and pre-formed any type of microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a c-di-GMP or any cyclic dinucleotide analogue thereof to inhibit any type of microbial colonization and any biofilm formation or to reduce any microbial colonization and any pre-formed biofilm on said solid surface. Therefore it is hard for one skilled in the art to determine if c-di-GMP or a cyclic dinucleotide analogue can be used in the method as set forth supra. The quantity of experimentation required to practice the invention as claimed would require studies of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization of all types of microbial pathogens. Since the specification fails to provide particular guidance for the method as set forth supra, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Nature of the invention. The claims are drawn to for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on S. aureus biofilm formation (see 00101), the effects of c-di-GMP on S. aureus pre-formed biofilms (00102), c-di-GMP treatment the prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine S. aureus (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see

00116), the effect of c-di-GMP treatment on S. aureus pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120).

The state of the prior art. The state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens. state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror

natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al 2006 Journal of Bacteriology Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1 and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract).

The art questions biofilm model systems and the factors that have to be considers as set forth supra. Therefore, given the lack of success in the art the state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens.

Guidance in the specification. The specification gives several examples of S. aureus bacteria in method for inhibiting microbioal colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or a cyclic dinucleotide analogue there of on pre-formed microbial biofilm or

biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3. Furthermore Example 4 discloses extracellular c-di-GMP increases. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). Therefore the specification fails to describe any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

In conclusion, the claimed invention is not enabled for any method for inhibiting any type microbial colonization and any type of biofilm formation or for reducing any type of colonization and pre-formed any type of microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a c-di-GMP or any cyclic dinucleotide analogue thereof to inhibit any type of microbial colonization and any biofilm formation or to reduce any microbial colonization and any pre-formed biofilm on said solid surface. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art questions biofilm model systems and the factors that have to be considers as set forth supra. Therefore, given the lack of success in the art the state of the art is unpredictable with regard to c-di-GMP and inhibiting or reducing colonization and biofilm formation in microbial pathogens. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-8, 10, 13-21 and 28-30 rejected under 35 U.S.C. 102(a) as being anticipated by Hook et al US Patent Application 20020169288 Date November 14, 2002.

Claims 1-8, 10, 13-21 and 28-30 are drawn to a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen (claim 1); A method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on said solid surface (claim 17).

Hook et al teach methods of treating or preventing a staphylococcal infection by administration of an effective amount of a GehD (analogue) composition to a human or animal (chicken i.e. bird) patient in need of such treatment (see abstract and 0050). Hook et al teach that antibodies (analogue) to GehD can be generated which can be useful in methods of treating or preventing staphylococcal infection such as bovine mastitis, and such antibodies can be used, such as in kits with suitable means to

identify binding, to determine the presence of the GehD protein and obtain information concerning the nature of an infection (see 0023, 0035). Analogue is defined as a structural derivative of a parent compound that often differs from it by a single element. Therefore any analogue can be applied to the limitation of cyclic dinucleotide analogue thereof.

Hook et al teach a method, wherein the strains are from S. aureus (see 0080). Hook et al teach, medical instruments or biological implants can be treated using the collagen-binding protein of the invention in order to reduce or eliminate the possibility of their becoming infected or further spreading a staphylococcal infection (see 0045). Hook et al teach a method of reducing staphylococci infection of an indwelling medical device or implant comprising coating the medical device or implant with a GehD lipase in an amount effective to reduce or inhibit binding of staphylococci to the medical device or implant (see claims). Hook et al teach the compositions may be effective against a variety of conditions, including use to protect humans against skin infections such as impetigo and eczema, as well as mucous membrane infections (see 0049). Hook et al teach when administered as pharmaceutical composition to a wound or used to coat medical devices or polymeric biomaterials in vitro and in vivo, both the proteins and the antibodies are useful as blocking agents to prevent or inhibit the binding of staphylococci to the wound site or the biomaterials themselves (see 0045).

Thus Hook et al teach a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, wherein the attenuation of the virulence of a microbial pathogen comprises treating a bacterial infection, wherein bacterial infection is a Staphylococcus aureus infection, wherein bacterial infection is mastitis, a Staphylococcus aureus infection of the mammary gland, wherein bacterial infection is treated by inhibiting microbial biofilm formation or by reducing the microbial already formed, wherein cyclic dinucleotide analogue thereof comprises a cyclic dinucleotide analogue thereof which acts as a c-di-GMP agonist, wherein microbial biofilm is

Staphylococcus aureus biofilm, wherein cyclic dinucleotide analogue thereof comprises a cyclic dinucleotide analogue thereof which acts as a c-di-GMP antagonist, wherein microbial biofilm is on the skin and mucosal surface, wherein bacterial infection is treated by inhibiting microbial biofilm formation or by reducing the microbial biofilm already formed.

Hook et al teach a method, wherein the inhibition or reduction of colonization of a microbial pathogen comprises treating a patient at risk of being colonized by a microbial pathogen or a patient already colonized by a microbial pathogen, wherein the colonization of a microbial pathogen that is inhibited or reduced is on a mucosal surface, wherein said microbial pathogen is Staphylococcus aureus, wherein said patient is a carrier of Staphylococcus aureus.

Hook et al teach a method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on solid surface, wherein solid surface is a solid surface of a medical device, wherein said medical device is implantable in or capable of attaching to a patient, wherein said medical device is implanted in a patient or otherwise in contact with a patient, wherein the microbial colonization and biofilm is Staphylococcus aureus colonization and biofilm and said c cyclic dinucleotide analogue thereof is or a cyclic dinucleotide agonist thereof, wherein said solid surface is a solid surface of a medical device, wherein said patient in need thereof is a mammal, wherein patient is in need thereof is human, wherein said patient in need thereof is a bird.

9. Claims 1-3, 5-8, 10-11, 13-21 and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Costerton et al US Patent 5,312,813 Date May 17, 1994.

Claims 1-3, 5-8, 10-11, 13-21 and 28 are drawn to a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an

effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen (claim 1); A method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on said solid surface (claim 17).

Costerton et al teach a method of killing microorganisms and a reduction method which form a biofilm on a tissue or implant surfaces in a patient (animal), by administering a biocide (analogue) (see abstract and Section C. Biofilm Reduction Method). Analogue is defined as a structural derivative of a parent compound that often differs from it by a single element. Therefore any analogue can be applied to the limitation of cyclic dinucleotide analogue thereof. Consterton et al teach several antibiotics administered in the method of killing microorganisms and a reduction method (see Summary). Costerton et al teach biofilm formation and colonization of S. aureus cells (see Example 3). Costerton et al teach the method of the invention used for reducing biofilms in vitro, by placing a biofilm containing surface in an electric field in the presence of biocide (see E. Applications). Costerton et al teach a body implantable device designed for use in biofilm reduction, with the treatment method of antibiotic administration accompanied by electric field generation by the indwelling catheter in an animal's urethra. Costerton et al teach that a device has one or more surfaces, or surface expanses which are exposed to body fluids, and on which biofilm formation can occur (see E. Applications and claims).

Thus Costerton et al teach a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, wherein the attenuation of the virulence of a microbial pathogen comprises treating a bacterial infection, wherein bacterial infection is a Staphylococcus aureus infection, the method further comprising administering an

antibiotic compound which is effective in treating bacterial infection, wherein bacterial infection is treated by inhibiting microbial biofilm formation or by reducing the microbial biofilm already formed. Costerton et al teach a method, wherein cyclic dinucleotide analogue thereof comprises c-di-GMP or a cyclic dinucleotide analogue thereof which acts as a c-di-GMP agonist, wherein microbial biofilm is Staphylococcus aureus biofilm, wherein said c-di- GMP or cyclic dinucleotide analogue thereof comprises a cyclic dinucleotide analogue of c-di-GMP which acts as a c-di-GMP antagonist, wherein said microbial biofilm is on a mucosal surface.

Consterto et al teach a method, wherein the inhibition or reduction of colonization of a microbial pathogen comprises treating a patient at risk of being colonized by a microbial pathogen or a patient already colonized by a microbial pathogen, wherein the colonization of a microbial pathogen that is inhibited or reduced is on a mucosal surface, wherein said microbial pathogen is Staphylococcus aureus, wherein said patient is a carrier of Staphylococcus aureus.

Consterto et al teach a method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on solid surface, wherein solid surface is a solid surface of a medical device, wherein said medical device is implantable in or capable of attaching to a patient, wherein said medical device is implanted in a patient or otherwise in contact with a patient, wherein the microbial colonization and biofilm is Staphylococcus aureus colonization and biofilm and said c cyclic dinucleotide analogue thereof is or a cyclic dinucleotide agonist thereof, wherein said solid surface is a solid surface of a medical device, wherein said patient in need thereof is a mammal.

10. Claims 1-3, 5-11, 13-19, 21, and 28-29 rejected under 35 U.S.C. 102(b) as being anticipated by Wooley et al US Patent Application 20020091074.

1-3, 5-11, 13-19, 21, and 28-29 are drawn to a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen (claim 1); A method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of c-di-GMP or a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on said solid surface (claim 17).

Wooley et al teach methods of inhibiting the proliferation of a microbial population of a surface lesion of a human or animal, wherein the lesion is contacted with an antimicrobial composition (analogue) comprising a pharmaceutically acceptable antibiotic. Wooley et al teach a method for administering an antimicrobial composition and medical dressing for delivering an antimicrobial composition to a site of a skin injury or lesion of a mammal, comprising a support and an antimicrobial composition (analogue), wherein the antimicrobial composition is at least one antimicrobial agent (see abstract see claims). Analogue is defined as a structural derivative of a parent compound that often differs from it by a single element. Therefore any analogue can be applied to the limitation of cyclic dinucleotide analogue thereof.

Wooley et al teach methods of the invention include bacterial species that may cause infections of a burn or lesion of the skin or oral mucosal lesion of a human or animal include, but are not limited to Staphylococcus aureus and Vibrio cholerae (see 0046). Wooley et al teach invention provides methods and devices for inhibiting an infection of a surface lesion of a human or animal, comprising and contacting a skin injury or surface lesion of a human or animal with an antimicrobial composition comprising a pharmaceutically acceptable antibiotic (see 0014).

Thus Wooley et al teach a method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of a

cyclic dinucleotide analogue thereof to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, wherein the attenuation of the virulence of a microbial pathogen comprises treating a bacterial infection, wherein bacterial infection is a Staphylococcus aureus infection, wherein bacterial infection is treated by inhibiting microbial biofilm formation or by reducing the microbial already formed, wherein cyclic dinucleotide analogue thereof comprises a cyclic dinucleotide analogue thereof which acts as a c-di-GMP agonist, wherein microbial biofilm is Staphylococcus aureus biofilm, wherein cyclic dinucleotide analogue thereof comprises a cyclic dinucleotide analogue thereof which acts as a c-di-GMP antagonist, wherein microbial biofilm is on the skin and mucosal surface, wherein bacterial infection is treated by inhibiting microbial biofilm formation or by reducing the microbial biofilm already formed.

Wooley et al teach a method, wherein the inhibition or reduction of colonization of a microbial pathogen comprises treating a patient at risk of being colonized by a microbial pathogen or a patient already colonized by a microbial pathogen, wherein the colonization of a microbial pathogen that is inhibited or reduced is on a mucosal surface, wherein said microbial pathogen is Staphylococcus aureus, wherein said patient is a carrier of Staphylococcus aureus.

Wooley et al teach a method for inhibiting microbial colonization and biofilm formation or for reducing colonization and pre-formed microbial biofilm on a solid surface, comprising exposing the solid surface to an effective amount of a cyclic dinucleotide analogue thereof to inhibit microbial colonization and biofilm formation or to reduce microbial colonization and pre-formed biofilm on solid surface, wherein solid surface is a solid surface of a medical device, wherein said medical device is implantable in or capable of attaching to a patient, wherein said medical device is implanted in a patient or otherwise in contact with a patient, wherein the microbial colonization and biofilm is Staphylococcus aureus colonization and biofilm and said c cyclic dinucleotide analogue thereof is or a cyclic dinucleotide agonist thereof, wherein said solid surface is a solid surface of a medical device, wherein said patient in need thereof is a mammal, wherein patient is in need thereof is human, wherein said patient in need thereof is a bird.

Status of the Claims

11. Claims 1-21 and 28-30 are rejected.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina Archie
Examiner
Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645